MEDSAFE
NEW ZEALAND MEDICINES
AND MEDICAL DEVICES
SAFETY AUTHORITY
A BUSINESS UNIT OF
THE MINISTRY OF HEALTH
www.medsafe.govt.nz

30 June 2011

Dear

Re: Dabigatran etexilate and the Intensive Medicines Monitoring Programme (IMMP)

Thank you for your letter of 22 June 2011, in which PHARMAC requests that Medsafe consider including dabigatran etexilate on the IMMP, based on a recent recommendation made by PTAC.

Medsafe notes that PTAC's rationale for recommending dabigatran be included on the IMMP is "to enable safety monitoring and collection of data given it is a new treatment in New Zealand and worldwide".

The IMMP is a prospective prescription event monitoring (PEM) study which is useful in confirming the safety profile of a medicine in general use (rather than in clinical trials) but it is not without its limitations. According to Shakir,[1] weaknesses of PEM studies include:

- Selection bias as not all questions sent to doctors are returned
- Time to results
- Dependence on reporting by doctors and therefore it can be good but no better than clinical notes
- Underreporting
- Restricted to general practice only
- No measure of patient compliance
- Lack of a comparator group
- Detection of rare adverse reactions not always possible even with cohorts of 10,000 to 15,000
- Subject to stimulation bias

[1] Shakir SAAW. Prescription Event Monitoring. In: Textbook of Pharmacoepidemiology. Strom BL & Kimmel SE. (Eds). 2006. John Wiley & Sons. West Sussex, England.

Medsafe considers that other more timely and effective pharmacovigilance tools can be better employed to facilitate the detection of emerging safety signals that may warrant regulatory action. This includes monitoring spontaneous adverse reaction reports both in the local context and internationally, reviewing findings from clinical and epidemiological studies and information provided to Medsafe by the manufacturer.

Reports of haemorrhagic events to dabigatran are an expected event and are consistent with the known safety profile dabigatran that was established at approval. An IMMP study may be able to quantify the rate of hemorrhagic events in the New Zealand population in general use, which would allow comparison with clinical trial data. However, in the absence of a comparator group, it would not be possible to determine whether these events occur at a higher incidence than available alternatives such as warfarin.

Dabigatran was approved for use in New Zealand in 2007, therefore Medsafe does not consider dabigatran to be a new medicine. The decision to approve dabigatran was based on evidence that demonstrated a favorable risk-benefit balance for the medicine in the indicated population. Major overseas medicine regulators have reviewed the same data and independently arrived at the same conclusion; dabigatran has been approved by the US Food and Drug Administration, the European Medicines Agency and the Australian Therapeutic Goods Administration. Dabigatran is therefore also available in major overseas markets.

At the time the decision was made to approve dabigatran, Medsafe did not consider there was a need to require the manufacturer to perform a specific post-market study to monitor the safety or effectiveness of the medicine. Since its approval, routine post-marketing surveillance activities by Medsafe have not identified any emerging safety issues in New Zealand or overseas that would suggest the risk-benefit profile of dabigatran may have changed. To date, Medsafe and other overseas medicines regulators consider the available evidence continues to support a positive risk-benefit balance for dabigatran.

Given the high level of interest by healthcare professionals in the safety of dabigatran following PTAC's recommendation to fund it, Medsafe will be closely monitoring the safety of this medicine. Medsafe intends to seek expert advice from the Medicines Adverse Reactions Committee on the current safety profile.

At present, Medsafe does not consider that a new safety signal has been identified by PTAC or that widening access warrants any regulatory action. The IMMP is not exclusive to Medsafe and therefore any body that wishes to contract an IMMP study is able to do so. Therefore this does not preclude PHARMAC from funding an IMMP study for its own purpose, for example to monitor the

effectiveness of its treatment guidelines or to monitor the concerns expressed by PTAC around the potential for off-label use.

Yours sincerely